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Perspective

Type 2 neuroimmune circuits in the shaping of physiology

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SUMMARY

Type 2 immune responses drive a broad range of biological processes including defense from large parasites, immunity to allergens, and non-immunity-related functions, such as metabolism and tissue homeostasis. The symptoms provoked by type 2 immunity, such as vomiting, coughing or itching, encompass nervous system triggering. Here, we review recent findings that place type 2 neuroimmune circuits at the center stage of immunity at barrier surfaces. We emphasize the homeostatic functions of these circuitries and how deregulation may drive pathology and impact disease outcomes, including in the context of cancer. We discuss a paradigm wherein type 2 neuroimmune circuits are central regulators of organismal physiology.

INTRODUCTION

Type 2 immunity is driven by the cytokines interleukin (IL)-4, IL-5, IL-9, and IL-13, which are associated with canonical adaptive T helper 2 (Th2) cells that contribute to the protection against helminths, allergens, and certain toxins. The discovery of group 2 innate lymphoid cells (ILC2s) advanced our understanding of type 2 responses in their broad diversity and scope. ILC2s were originally identified as important cellular players that confer protective immunity to helminth infections, notably caused by *Nippostrongylus brasiliensis*.[1–6] ILC2s are tissue-resident lymphocytes constituting the major source of innate IL-5 and IL-13 downstream of microenvironmental signals, such as epithelial and mesenchymal cell-derived IL-33, IL-25, and thymic stromal lymphopoietin (TSLP).[1–8] In addition to their role in protective type 2 immunity, ILC2s perceive and integrate local tissue status, forming building blocks of tissue homeostasis, even in the absence of infection.[9–18]

ILC2s engage into direct and indirect interactions with the nervous system, thus acting as relaying stations of neuronal tones in a diversity of tissues and organs.[16,19–26] Neuro-ILC2 interactions can mediate defense to infection, modulate allergic responses, and promote tissue repair and homeostasis, amongst others (reviewed in Chesne et al.[27]). Type 2 neuroimmune circuits can be also activated in response to external environmental perturbations (e.g., dietary stress, allergens, temperature differences, light/dark cycles) indicating that, in addition to perceiving local tissue signals, type 2 neuroimmune axes integrate distant internal states and external environmental cues.[25,28–32] Thus, direct and indirect type 2 neuroimmune interactions form critical hubs that integrate local, distant, and external states, triggering type 2 responses that sustain organismal homeostasis.

In this article, we review evidence that has placed type 2 neuroimmune circuits at the center stage of mucosal immunity. We emphasize homeostatic functions of these circuitries and discuss how important biomedical research topics might be targets of neuroimmune regulation. Lastly, we discuss a model in which type 2 neuroimmune circuits evolved as innate homeostatic rheostats, co-opting protective immunity functions throughout evolution. Thus, we propose that type 2 pathways emerged to maintain functional integrity in tissue physiology, being later co-opted to protect the host during parasite infections.

TYPE 2 NEUROIMMUNE RESPONSES IN INFECTION

The nervous system is equipped to detect and respond to external stimuli provoked by bacteria, fungi, and parasites (reviewed in Veiga-Fernandes and Mucida and Veiga-Fernandes and Pachnis[33,34]). For example, dermal nociceptive sensory neurons (see Box 1 for glossary of terms) express Toll-like Receptor 7 (TLR7) that can mediate itch;[35,36] enteric neurons express TLR2 and TLR4;[37–39] enteric glial cells express TLR2, TLR3, TLR4, and TLR7;[38,40–42] enteric glial cells and cholinergic neurons rely on myeloid differentiation primary response 88 (MYD88) to sense bacterial and helminth excretory-secretory products, in turn secreting neuronal peptides that induce strong ILC responses.[19,43] Reciprocally, when confronted to type 2 inflammation settings, the nervous system can trigger itch, cough, diarrhea, and vomiting, which can facilitate the expulsion of parasites, amongst others[44] (and reviewed in Klein Wolterink et al.[32]).

Neuronal signals shape innate type 2 protective immunity at mucosal barrier sites. For example, during *Nippostrongylus brasiliensis* infection, cholinergic neurons sense helminth products in the lung and intestine[19] and secrete neuromedin U (NMU) that promotes anti-parasitic type 2 innate cytokine expression in an NMU receptor 1 (NMUR1)-dependent manner.[19,22,25] Activated ILC2s increase expression of choline acetyltransferase (ChAT), an enzyme central to the biosynthesis of acetylcholine, which increases ILC2 function in an autocrine and paracrine manner.[20,45] Cholinergic neurons are also capable of dampening ILC2 function via α7 nicotinic acetylcholine receptor (α7nAChR).[21] Activation of the sympathetic nervous system (SNS) was also shown to hamper anti-parasitic innate

Box 1. Glossary

Nociceptor sensory neurons: sensory neurons that are activated by noxious or damaging stimuli. Nociceptor neurons are classified according to their ability to respond to mechanical, thermal, and chemical stimuli. Free nerve endings in the periphery serving as receptive sites extend from neuronal cell bodies in the dorsal root or cranial nerve ganglia.
Enteric neurons: neurons located in the intestine that are part of the enteric nervous system. The enteric nervous system is a large division of the peripheral nervous system that can control gastrointestinal behavior independently of central nervous system input.
Enteric glial cells: enteric glial cells are a type of peripheral glia that are similar to astrocytes of the central nervous system. Amongst other functions, they maintain the structural integrity of the nervous system, provide trophic support to neurons, insulate one neuron from another, and can clear debris.
Cholinergic neurons: neurons that release acetylcholine. These include all preganglionic fibers of the autonomic nervous system, both sympathetic and parasympathetic systems; all postganglionic fibers of the parasympathetic system; and sympathetic postganglionic fibers innervating sweat glands.
Peripheral nervous system (PNS): the peripheral nervous system is composed by the autonomic nervous system, which controls involuntary bodily functions; and the somatic nervous system that controls muscle movement and relays information from ears, eyes, and skin to the central nervous system.
Autonomic nervous system (ANS): the autonomic nervous system is part of the peripheral nervous system. It contains three anatomically distinct arms: sympathetic, parasympathetic, and enteric.
Sympathetic nervous system (SNS): sympathetic neurons are normally assumed to be part of the peripheral nervous system, but many of these neuronal cell bodies are present in the central nervous system. Sympathetic neurons of the spinal cord communicate with peripheral sympathetic neurons. In response to these stimuli, postganglionic neurons release catecholamines that bind adrenergic receptors on target cells inducing "fight-or-flight" responses.
Parasympathetic nervous system: the parasympathetic system is responsible for stimulation of "rest-and-digest" or "feed-and-breed" activities. Its action is described as being complementary to that of the sympathetic nervous system.
Enteric nervous system (ENS): the enteric nervous system is a large division of the peripheral nervous system that can control gastrointestinal behavior independently of central nervous system input.
Central nervous system (CNS): the central nervous system is essentially composed by the brain and spinal cord.
Vagus nerve: the vagus nerve allows for connection between the brainstem and the body. The vagus nerve functions contribute to the autonomic nervous system, which consists of the parasympathetic and sympathetic arms.
Brainstem: the brainstem is the structure that connects the cerebrum of the brain to the spinal cord and cerebellum. It is composed of three sections in descending order: the midbrain, pons, and medulla oblongata. It is responsible for many vital functions of life, such as breathing, consciousness, blood pressure, heart rate, and sleep.
Pulmonary neuroendocrine cells: these are specialized epithelial cells that are present in the airways. Neuroendocrine cells can be found as solitary cells or associated in cell clusters called pulmonary neuroepithelial bodies. Neuroendocrine cells receive neuronal input that controls release of endocrine molecules.
Paraventricular nucleus of the hypothalamus (PVH): the hypothalamic paraventricular nucleus is located in the hypothalamus and plays a critical role in neuroendocrine, autonomic, and behavioral regulation by controlling the activity of key hypothalamic-pituitary-target organ systems. The paraventricular nucleus of the hypothalamus has been involved in the control of stress, metabolism, growth, reproduction, immune system functions, amongst others.

responses. Notably, treatment of helminth-infected mice with a β2-adrenergic receptor agonist limits type 2 inflammation and increases worm burden, while deletion of β2-adrenergic receptor leads to exacerbated ILC2 responses.[23] Vasoactive intestinal peptide (VIP) has been shown to potentiate the ILC2 effector functions.[28,46] In the context of the helminthic infection with Trichurius muris, the deletion of the VIP receptor 2 (Vipr2) specifically in ILC2 results in elevated worm burden and enlarged caeca when compared with wild-type littermates.[46]

The outcome of innate type 2 inflammation is also fine-tuned by the neuropeptide α-calcitonin gene-related peptide (CGRP). CGRP inhibits the actions of NMU and IL-33 on ILC2-derived IL-13 production and ILC2 proliferation, while promoting IL-5 production.[24] Thus, neurotransmitters and neuropeptides are critical rheostats of type 2 innate immunity by activating, suppressing, and defining the magnitude and outcome of such responses.

It has been suggested that parasitic helminths evolved to promote local responses that facilitate their own maintenance rather than their eradication by type 2 immunity.[9,17] For example, primary helminth infections induce gut neuronal protection during subsequent infection with the same pathogen. This neuroprotective response relies on eosinophil-derived IL-4 and IL-13 and highlights the importance of neuroimmune circuits in sustaining host fitness and tissue tolerance during helminth infections.[47]

In addition, activation of the SNS, which is known to promote lipolysis,[48] energy expenditure, metabolic function, and mobilization of nutrients,[16,48] positively impacts parasitic colonization and survival.[23] Reciprocally, humans that are recurrently infected by helminths in developing countries, display improved metabolic function.[49] Thus, it is well possible that the functions associated with parasitic immunity were co-opted from pre-existing homeostatic functions by type 2 lymphocytes. Nevertheless, the circuitries and mechanisms by which type 2 neuroimmune

responses are tuned to integrate distinct arms of the autonomic nervous system in a time-resolved manner (i.e., sympathetic, parasympathetic, and enteric) remain largely undefined.

Neuroimmune hubs in allergic responses

Dysregulated type 2 immune responses provoked by environmental allergens are at the heart of allergy, notably atopic dermatitis, allergic asthma, food allergies, and anaphylaxis. The key immunological players in this type of responses include T helper 2 (Th2) cells and ILC2s, which secrete type 2 cytokines and activate B lymphocytes to switch to immunoglobulin E (IgE) production. Type 2 cytokines also recruit T cells and eosinophils to the sites of allergic inflammation. In addition, mast cells and dendritic cells (DCs) are active players in the allergic inflammatory circuits[17] (see review by Molofsky and Locksley in this issue[50]).

The involvement of the nervous system in allergic responses has been investigated for more than 60 years. Dekker et al. established that classical Pavlovian conditioning in patients suffering from asthma can result in similar allergic reactions in the absence of the allergen.[51] Notably, patients who experienced asthma attacks following exposure to house dust extract and grass pollen developed similar symptoms after inhalation of the neutral solvent used to deliver the allergens. The link between behavior and immune function in allergy suggested bidirectional crosstalk between the nervous and the immune systems. Nevertheless, only recent work has begun to decipher neuroimmune mechanisms in allergic responses. Florsheim et al. uncovered that ingestion of allergens by rodents activates specific brain areas (such as nucleus tractus solitarius, parabrachial nucleus, and central amygdala) that promote aversive behavior.[52] Such reaction requires the presence of IgE antibodies and mast cells, further confirming that the immune component is crucial in driving behavioral aversion to noxious stimuli. Type 2 cytokines can also regulate neuronal function in the context of atopic dermatitis. Mechanistically, IL-4 receptor alpha (IL-4Rα) acts directly on murine and human sensory neurons to trigger itch and, as a consequence, influences the behavior.[44]

Nociceptor sensory neurons amplify immune responses and potentiate allergic inflammation in the context of the allergic airway inflammation. Activation of pulmonary sensory neurons results in increased calcitonin gene related peptide (CGRP) release and type 2 immune cell infiltration. Reciprocally, immune cell-derived IL-5 acts on sensory neurons leading to increased VIP that stimulates type 2 immunity, thus creating a positive feedback loop that promotes allergy.[30] House dust mites also activate nociceptor neurons in the skin and, as a result, promote degranulation of mast cells.[53] This early inflammatory circuit has been specifically attributed to nociceptive sensory neurons that express ion channels TRPV1 and Tac1 and to mast cells expressing Mas-related G-protein-coupled receptors member B2 (MRGPRB2). Such neuroimmune cell unit senses allergen-associated cysteine-like proteolytic activity and drive type 2 skin inflammation.[34,53] Allergen-activated TRPV1 neurons in the skin can also release substance P and promote migration of CD301b DCs via the engagement of the MRGPR member A1 (MRGPRA1).[54] As such, sensory neurons play a critical role in allergen recognition, mast cell degranulation, and DC activation, constituting essential early activators of allergic immune responses.

Allergens introduce perturbations to tissue physiology, leading to maladaptive responses that result in activated neuroimmune type 2 circuitries that amplify allergic responses. It is therefore tempting to speculate that silencing nociceptors might be a useful therapeutic strategy to treat type 2 allergic inflammation. In agreement, silencing mouse airway sensory neurons with QX-314, a charged sodium channel inhibitor that specifically blocks nociceptors, substantially reduces house dust mite-induced airway inflammation and bronchial hyperresponsiveness.[30] Nevertheless, the role of sensory neuroimmune responses in human allergy settings remains poorly explored. While the importance of direct neuroimmune interactions in infection and allergy are now well documented, the relevance of indirect neuroimmune communication, notably via epithelial intermediates, started to be appreciated only more recently.

Neuro-epithelial sensors and type 2 responses

A large number of type 2 responses occur at barrier surfaces, where epithelial cells, neurons, and immune cells sense their environment and modulate local immune functions. Epithelial cells react to tissue perturbations by secreting ample amounts of alarmins: IL-33, TSLP, and IL-25 are critical triggers and effectors in type 2 responses.[55–58] IL-33 expression by human epithelial cells is increased in bronchial asthma,[57] and specialized skin epithelial cells, keratinocytes, actively release IL-33 upon stimulation with inflammatory stimuli *in vitro*.[59] Interestingly, both murine and human dorsal root ganglia (DRG) express the IL-33 receptor (IL-33R).[60,61] Deletion of IL-33R in sensory neurons reduces the responsiveness to stimuli that generates dry skin itch.[61] Furthermore, keratinocyte-derived TSLP acts on sensory neurons to promote itch via the TSLP receptor (TSLPR) in a mast cell- and lymphocyte-independent manner.[62]

Bidirectional communication between neurons and epithelial cells, i.e., neurons signaling directly to epithelial cells and the latter communicating back to neurons, have not been formally demonstrated in the context of type 2 responses. However, a neuroepithelial circuit was shown to convey nutritional states by connecting the gut lumen to the central nervous system (CNS) in just one synapse.[63] Notably, enteroendocrine cells synapse with neurons of the vagus nerve to transduce gut luminal signals using glutamate as a neurotransmitter, in turn, vagal neurons connect to the brainstem, conveying temporal and topographical intestinal sensing information into the brain. Tuft cells, a group of specialized chemosensory cells in the enteric epithelial-lining, respond to the Tritrichomonas-derived metabolite succinate and activate ILC2 via IL-25.[13] Tuft cells express high amounts of the enzyme ChAT, required for acetylcholine production.[11] In addition, these chemosensory cells are found in a close proximity to neurons,[64] suggesting that neuron-tuft cell interactions may regulate enteric type 2 responses.

Pulmonary neuroendocrine cells (PNECs) are rare innervated epithelial cells organized in neuroendocrine bodies. PNECs act as tissue sensors and modulate immune responses via production of neuropeptides.[65,66] In response to ovalbumin sensitization or house dust mite, PNECs produce CGRP and gamma-aminobutyric acid (GABA). As a consequence, CGRP triggers ILC2 activation while GABA induces goblet-cell hyperplasia.[66] Thus, this PNEC-ILC2 relay system is an important hub that amplifies asthma reactions.

Research in the space of peripheral neuronal interactions with other body systems has mostly focused on two-partite circuits, notably neuroepithelial or neuroimmune crosstalk hubs during tissue perturbations.[18,26] However, organ homeostasis relies on orchestrated multi-tissue hubs that ensure complex physiological processes. Thus, it is likely that tripartite neuro-epithelial-immune circuits operate to drive type 2 responses and tissue homeostasis at mucosal barriers. For example, how do neuroepithelial sensors integrate gut microbial and metabolite status to regulate type 2 tones in the intestine? How do neuroendocrine axes regulate type 2 immunity and how can the latter tune organismal neuroendocrine circuits? Finally, type 2 neuroimmune and neuroepithelial circuits were mostly explored in the context of infection and allergy, but how these circuits shape chronic tissue perturbations (e.g., cancer, aging) is a challenge to be tackled in the years to come.

TUMORS, NERVES, AND TYPE 2 REGULATORS

The tumor microenvironment (TME) is comprised of mesenchymal cells, vasculature, immune cells, nerve cells, and the extracellular matrix. Tumors can recruit peripheral neurons to the TME. Such intra-tumoral nerve infiltration occurs mostly in highly innervated organs and is associated with poor prognosis in clinical studies.[67–69] Sympathetic denervation slows the growth of tumors in the murine skin and has inhibitory effect on the progression of neuroblastoma and breast adenocarcinoma in mice.[70,71] Peritumor innervation impacts the components of the TME, including immune cells. Sympathetic denervation of tumors using adenovirus-induced diphtheria toxin A (DTA) in tyrosine hydroxylase (TH) neurons results in the decreased expression of the immune checkpoint molecules programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) in human breast cancer xenografts.[72] Activation of beta-adrenergic signaling recruits macrophages to the tumor parenchyma and induces expression of M2-like genetic signatures and is associated with increased metastatic potential in an orthotopic model of breast cancer, suggesting that blocking this neuro-immune circuit may restrict cancer progression.[73] In human gastric cancer, tumor-derived adrenomedullin, a neuropeptide with anti-apoptotic and anti-inflammatory effects, induces degranulation of mast cells and promotes cancer progression.[74]

Type 2 immune responses present potential therapeutic targets in various cancers. Peritumoral infiltration of mast cells is associated with a poor survival outcome in several cancers after resection.[74–76] Tumor-derived IL-33 has a stimulatory effect on mast cells, which recruit macrophages to the TME and promote gastric cancer expansion in mice and humans.[77] Interestingly, IL-33 has a beneficial role in tumor immunity in other contexts. In murine models, IL-33-driven recruitment of eosinophils can dampen melanoma growth[78]; in addition, tumor-linked eosinophilia is associated with a favorable prognosis in human oral squamous cell carcinomas.[79] Innate IL-5 attracts eosinophils to the TME, thus promoting anti-tumor immunity in lung metastatic melanoma.[80] Importantly, IL-5-producing ILC2s accumulate in human pancreatic adenocarcinoma (PDAC), and tumor-infiltration by ILC2 correlates with increased survival in mouse PDAC models.[81] In murine models of colon cancer, the presence of ILC2 within tumors associates with slower tumor progression in a manner dependent on ILC2-derived IL-9.[82] The impact of ILC2 may be context dependent. In human and mouse colon cancer, the IL33-ILC2-IL13 axis sustains migration and invasiveness of cancer cells, highlighting a pro-tumorigenic role of ILC2.[83] Thus, it is likely that diverse tumor environment triggers distinct ILC2 programs in a time-, space-, and context-dependent manner, ultimately shaping tumor progression. For example, how peri- and intra-tumoral neurons regulate innate type 2 responses and tumor progression? How tumor innervation conveys body state information to tumor infiltrating type 2 cell?

More than 40 years ago, researchers asked whether targeting specific brain regions might influence tumor growth.[84,85] Bilateral electrolytic lesions of the median eminence area of the hypothalamus inhibited liver carcinogenesis in male rats.[85] Using poly I:C and camphor odor as a conditioning stimulus, it was shown that sequential exposure to the camphor affected natural killer (NK) cell activity and tumor growth in a murine model of multiple myeloma.[86] These classical studies indicate a brain-body communication that modulates cancer growth possibly via triggering cancer immunity. More recently, it has been shown that sensory neurons directly dampen anti-tumor cytotoxic T cells via CGRP in a mouse model of melanoma.[87]

Overall, while T2 immune response and neuronal signals can impact tumor grown and progression to metastasis in different settings, whether and how the nervous and the immune system interact in the context of cancer and how this varies in distinct disease context or during tumor evolution will require more in-depth understanding of these circuits.

Type 2 neuroimmune circuits and organismal homeostasis

Tissue homeostasis is maintained by a collection of multi-tissue interactions that regulate specific variables within the tissue environment. Such complex interactions rely on internal and external signals that are detected by sensor cells (e.g., neuronal, epithelial, immune, etc.) that relay information to effector cell types in discrete tissues (reviewed in Meizlish et al.[88]). Type 2 responses constitute clear examples of sensor and effector cells that maintain several homeostatic processes. For example, whereas obesity and insulin tolerance are associated with adipose type 1 inflammation,[89] in a lean, healthy state, the white adipose tissue (WAT) is predominantly populated by eosinophils, ILC2s, and T regulatory (Treg) cells that sustain M2-like macrophages.[10,90,91] Eosinophils, type 2 cytokines, and M2 macrophages stimulate the thermogenic capacities of WAT.[12,92] As such, adipose type 2 regulatory circuits have been attracting a lot of attention, holding promise as novel therapeutic targets to improve thermogenic capacity and insulin sensitivity in humans[93] (see review by Pearce et al. in this issue[94]).

Type 2 neuroimmune circuits operate at the organismal level to regulate adipose homeostasis and energy expenditure. High-order hypothalamic neurons, notably in the paraventricular nucleus of the hypothalamus (PVH), connect to visceral adipose sympathetic neurons, which in turn instruct mesenchymal cells to activate adipose-resident ILC2. Then, innate type 2 cytokines promote energy expenditure by adipocytes.[16] Such long-range circuitry maintains visceral adipose tissue homeostasis and disruption of said axis results in metabolic imbalance and

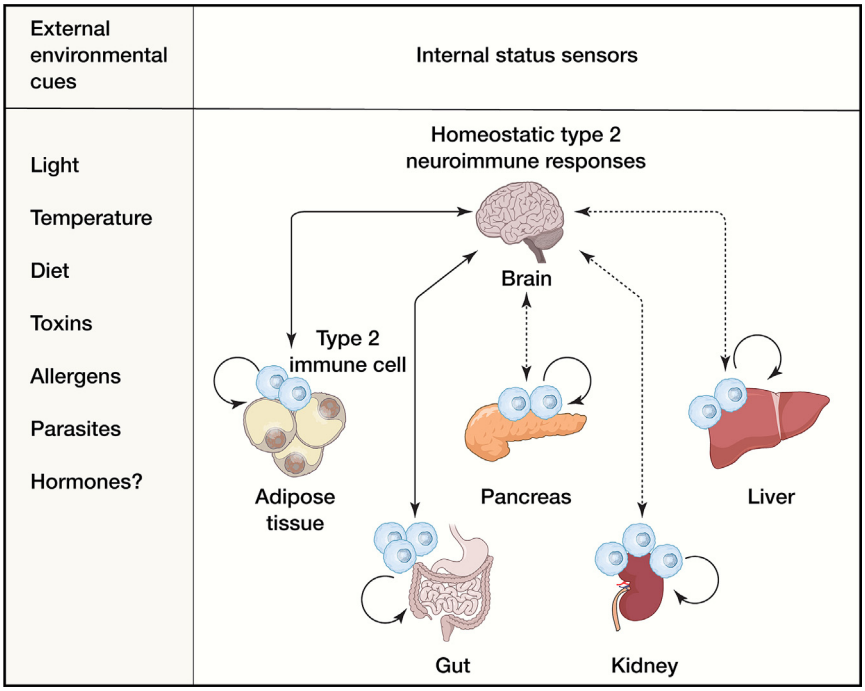

Figure 1. Homeostatic type 2 neuroimmune circuits shape organismal physiology

We propose that type 2 pathways emerged to maintain tissue physiology being co-opted during parasite infections. Type 2 cells innately form the building blocks of tissue physiology, perceiving local tissue cues that are relayed between other organs and systems (detailed graphical representation of cellular and molecular mechanisms can be found elsewhere[26,32]). In addition, the bidirectional connection between type 2 immune cells and the nervous system empowered type 2 neuroimmune axes with the unique capacity to efficiently perceive, integrate, and respond to ever changing external environmental perturbations (e.g., allergens, temperature differences, light/dark cycles). Our model proposes that, direct and indirect neuroimmune interactions form critical hubs that integrate local, distant, and external states, triggering type 2 homeostatic responses that sustain organismal physiology.

obesity. This brain-adipose axis further illustrates a tripartite neuro-mesenchyme-immune circuit that senses and responds to internal signals to promote metabolic homeostasis.[16] As such, it is tempting to speculate that akin type 2-centered homeostatic circuits operate in other organs to regulate diverse physiological processes.

In the skin, murine ILC2s are a critical component of the thermoregulation machinery. Stimulation of the cold-sensing receptor TRPM8 provokes increase in IL-18 production and subsequent activation of CD81$^+$ ILC2 and thermogenesis in the skin.[95] Although TRPM8 is highly expressed by cold-sensing neurons, the contribution of TRPM8$^+$ keratinocytes to the skin thermoregulation remains to be established. In addition, the cellular sources of IL-18 also need to be studied. In this regard, the enteric nervous system-derived IL-18 has been reported to drive an anti-microbial program in the context of gut *Salmonella* infection.[96] Whether similar molecular sensors are present in skin neurons is still unknown.

In the kidney, pre-treatment with IL-33 alleviates the symptoms of renal fibrosis in a unilateral ureteral obstruction model.[97] This protective effect is observed in the absence of CD4 T cells, pointing to a central contribution by ILC2 in this disease model.[97] In contrast, ILC2-deficiency, ILC2-depletion, or ILC2-reduction does not impact the outcome of acute kidney injury.[98] In a murine model of heart injury, ILC2s respond promptly to injury by rapid expansion and secretion of IL-4.[99] A cardioprotective effect of type 2 responses is attributed to IL-33-responsive ILC2 in the context of catecholamine-induced stress cardiac injury.[100] Although heart failure is associated with dysfunction of the autonomic nervous system (ANS),[101] neuroimmune regulation may also play important roles in this setting.

Meningeal immune repertoires are dominated by type 2 circuits.[102] Spinal cord injury (SCI) potentiates type 2 inflammation in meningeal spaces and has a potent effect on meningeal ILC2 activation.[103] In the context of the SCI, the adoptive transfer of ILC2 into the cerebrospinal fluid-filled space (cisterna magna) of ST2 deficient mice one day before the injury has beneficial effects on animal recovery.[103] Given that ILC2s are capable of mounting very rapid responses to environmental signals, it is tempting to speculate that they are major innate rheostats of type 2 cytokine-dependent mechanisms in the brain and brain-body axes.

Type 2 neuroimmune axes operate at the tissue, organ, interorgan, and organismal level. Thus, it is likely that the neuroimmune interactome also intersects with other major homeostatic systems, such as the endocrine and cardiovascular systems. For example, associations between stress and allergic disorders have been recognized for decades in clinical practice.[104] Similarly, stress is known to also have a substantial impact on energy metabolism and metabolic homeostasis.[105] Nevertheless, how stress-related hormones interact with type 2 neuroimmune responses to preserve tissue homeostasis is still unclear.

The study of peripheral neuroimmune interactions is a fast evolving, bourgeoning field. But what are the rules and principles that govern homeostatic type 2 neuroimmune responses? Cardoso et al. recently revealed that the PVH is the major hub regulating brain-derived sympathetic flow into the visceral AT where innate type 2 responses are triggered to regulate the host metabolism.[16] Therefore, it is possible that neuroimmune circuits follow a pyramidal hierarchical tree, whereby panoplies of tissue neuroimmune hubs interconnect with far less abundant high-order circuits to regulate tissue and organismal homeostasis (Figure 1). In this scenario, additional brain areas are expected to feed into other organ- or process-specific type 2 neuroimmune circuits. In agreement, it was recently shown that insular cortex neurons can trigger enteric immune responses.[106,107]

In sum, it is likely that type 2 neuroimmune circuits evolved as innate homeostatic rheostats, co-opting protective immunity functions throughout evolution. Thus, we propose that type 2 pathways emerged to maintain tissue physiology, being later

co-opted to protect the host during parasite infections. Indeed, type 2 immunity is predominant in several tissues (e.g., adipose tissue, meninges) in the absence of pathogenic infection or exogenous stimuli.[10,90,91,102,103,108] In agreement, local and long-range type 2 neuroimmune circuits were shown to operate at the organ and organismic level to regulate nutritional and metabolic homeostasis.[16,28]

CONCLUDING REMARKS

Type 2 neuroimmune circuits have only recently caught the attention of the immunology community. In the past decade, research in this space has rapidly evolved, challenging previous concepts and bringing to bear new type 2 response modalities that shape local and organismal homeostasis. Technology advancements, such as intravital multiphoton microscopy, tissue clearing coupled to high-resolution light-sheet microscopy, neuronal activation methods, and/or single-cell RNA sequencing have contributed immensely to the understanding of neuroimmune communication at the tissue and organismal levels. Here, we described type 2 neuroimmune circuits in mucosal immunity; we emphasized homeostatic functions of these circuitries; and we discussed how other research areas might be targets of neuroimmune regulation. However, many challenges remain ahead. For example, helminth infections, allergens, and metabolic homeostasis require similar type 2 neuroimmune responses that are controlled by akin molecules, but how these multi-tissue, inter-organ axes interact in a time-, space-, and context-dependent manner remains poorly explored. Understanding how type 2 neuroimmune responses shape human physiology is also an important endeavor for the decades to come.

Type 2 neuroimmune circuits have been described at the tissue, organ, inter-organ, and organismal levels. The broad distribution of these type 2 neuroimmune circuits strongly suggests their intersection with other homeostatic systems, e.g., endocrine, cardiovascular, putting the "neuroimmune system" at the centerstage of organismal physiology. Thus, we propose that type 2 responses emerged to maintain tissue physiology, being later co-opted to protect the host during parasite infections.

In the forthcoming years, it is our expectation to witness type 2 neuroimmune axes as important targets in conditions such as metabolic syndrome, kidney injury, heart diseases, and cancer. Nevertheless, and until we get there, it is crucial to uncover, with molecular and cellular detail, the neuroimmune interactome that sustains body physiology.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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